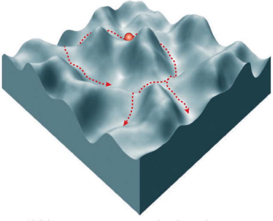
Taming Asynchrony for Attractor Detection in Large Boolean Networks



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Biological background & motivations

Cell potency

Cell potency is a cell's ability to differentiate into other cell types.

- Embryonic stem cells: pluripotent – have the potential to differentiate into any of the three germ layers: endoderm, mesoderm, or ectoderm.
- Stem cells derived from adult tissues: multipotent – maintain a limited, tissue-specific, regenerative potential

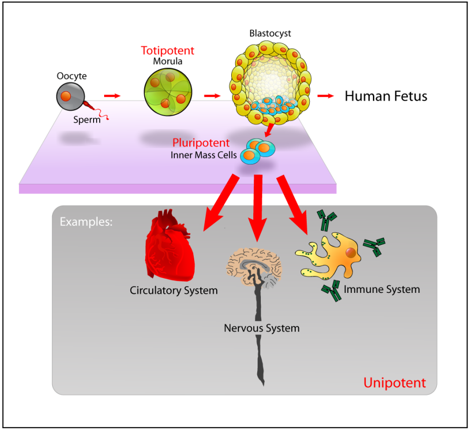
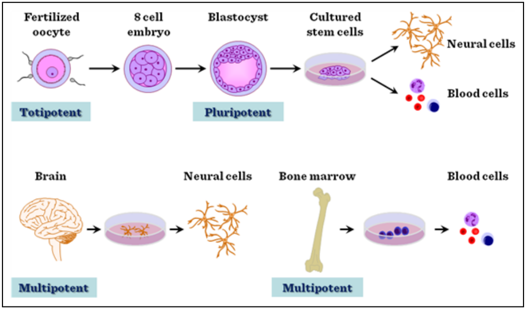


Image: Wikipedia

Cellular reprogramming

- Reprogramming of differentiated adult cell to embryonic-like pluripotent state
- Reprogramming to other adult cell types without intermediate reversion to a pluripotent state



D. Bartis and J. Pongrácz. Three dimensional tissue cultures and tissue engineering. University of Pécs, 2011.

Cellular reprogramming

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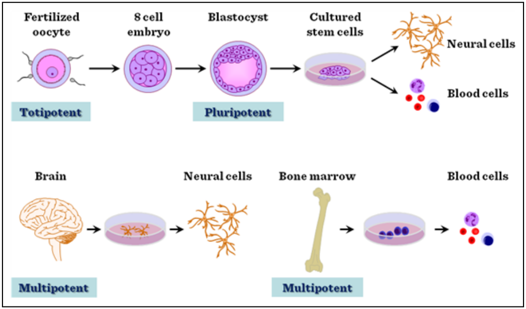


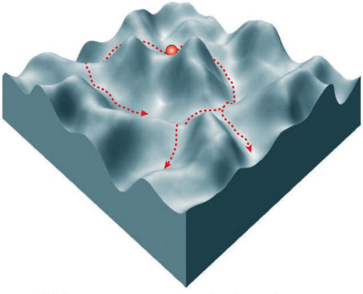
D. Bartis and J. Pongrácz. Three dimensional tissue cultures and tissue engineering. University of Pécs, 2011.

Disease modelling, drug design, organ synthesis, tissue repair, etc.

Conrad Waddington's epigenetic landscape

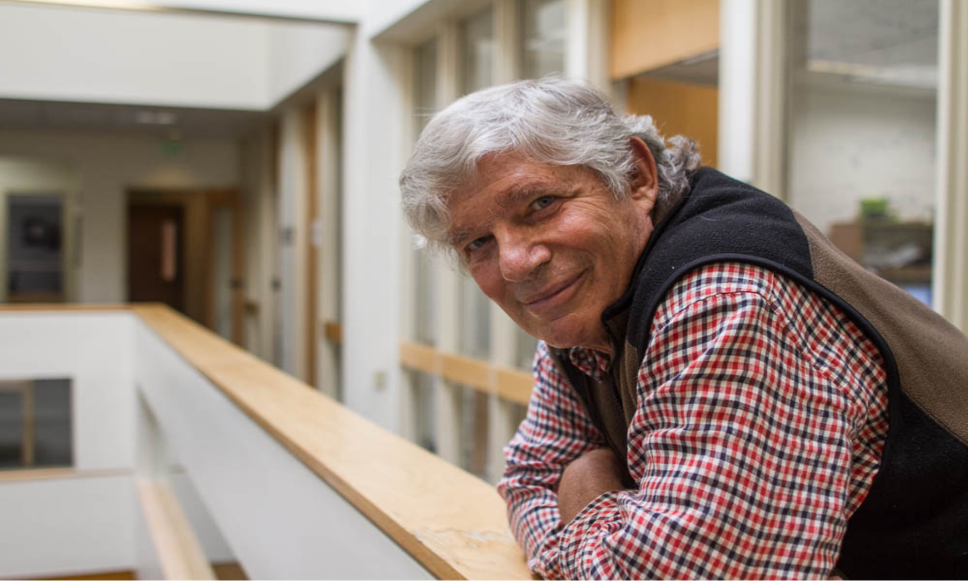
- A visual metaphor for the embryonic development and cellular commitment
- Development viewed as a ball rolling down a sloping landscape containing multiple 'hills' and 'valleys'
- Cells take different paths down this landscape and so adopt different fates
- Hills act as barriers by separating the landscape into valleys (cell types)
- Differentiation is not terminal: epigenetic barriers that can be overcome given sufficient perturbations

Epigenotype – *"complex network of processes and causal mechanisms by which the genes of the genotype bring about phenotypic effects".*

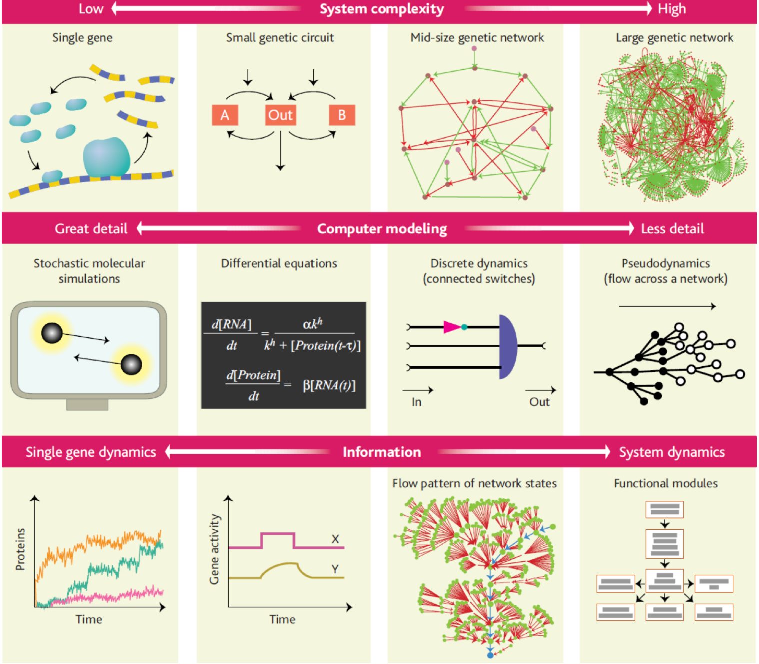


$$\boxed{\text{Phenotype} = \text{genotype} + \text{epigenotype} + \text{environment}}$$

Image: B. D. MacArthur et al. *Nature Reviews Molecular Cell Biology*, 10(10):672–681, 2009.



The idea that cell types may be related to 'balanced states' of an underlying regulatory system bears a striking resemblance to the modern mathematical notion of attractors of dynamical systems.



S. Bornholdt. Less Is More in Modeling Large Genetic Networks. Science, 310(5747):449-451, 2005

Boolean networks (BNs)

Boolean networks

Boolean networks are a class of discrete dynamical systems that can be characterised by interactions over a set of Boolean variables.

- First introduced by Stuart Kauffman in 1969 as a simple model class for studying dynamical properties of gene regulatory networks.
- Assumption: genes can be in two possible states of activity (e.g., ON or OFF) at any given point in time, and that they act on each other by means of Boolean functions.

Boolean networks

- A Boolean network $G(V, \boldsymbol{f})$ is defined as a set of binary valued variables (also referred to as nodes or genes), $V = \{x_1, x_2, \ldots, x_n\}$ and a vector of Boolean functions $\boldsymbol{f} = (f_1, f_2, \ldots, f_n)$.
- At each time point t, the state of the network is defined by the vector $\boldsymbol{x}(t) = (x_1(t), x_2(t), \ldots, x_n(t))$, where $x_i(t)$ is the value of variable x_i at time t, i.e., $x_i(t) \in \{0, 1\}$.
- For each variable x_i, there exists a predictor set $\{x_{i_1}, x_{i_2}, \ldots, x_{i_{k(i)}}\}$, and a Boolean predictor function (or simply predictor) f_i being the i-th element of $\boldsymbol{f}$ that determines the value of x_i at the next time point, i.e.,

$$x_i(t+1) = f_i(x_{i_1}(t), x_{i_2}(t), \ldots, x_{i_{k(i)}}(t)),$$

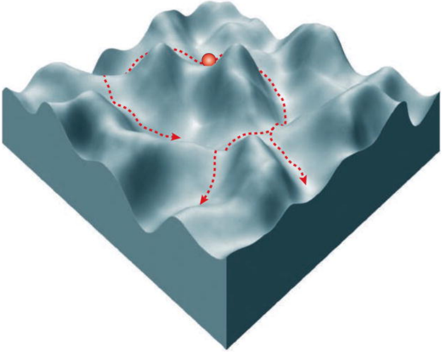
where $1 \leq i_1 < i_2 < \cdots < i_{k(i)} \leq n$.

Synchronous Boolean networks: Attractors

$$\boldsymbol{x}(t+1) = \boldsymbol{f}(\boldsymbol{x}(t))$$

- Given an initial state, within a finite number of steps, the BN will transition into: a fixed state, called singleton attractor, or a set of states through which it will repeatedly cycle forever, referred to as cyclic attractor.
- The attractor structure of a BN is determined by the particular combination of singleton and cyclic attractors, and by the cycle lengths of the cyclic attractors. The attractors of a BN characterise its long-run behaviour.
- The states that lead into an attractor constitute its basin of attraction. The basins form a partition of the state space.

Attractor detection for large asynchronous BNs



BDD-based attractor detection for asynchronous BNs

The asynchronous updating scheme: $T(x(t), x(t+1))=$

$$\Big(x_i(t+1) \leftrightarrow f_i(x_{i_1}(t), x_{i_2}(t), \cdots, x_{i_{k_i}}(t))\Big) \bigwedge_{j\neq i}(x_j(t+1) \leftrightarrow x_j(t))$$

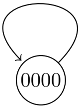
It states that node v_i is updated by its Boolean function and other nodes are kept unchanged.

BDD-based attractor detection for asynchronous BNs

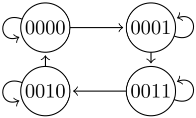
[Attractor of a BN] An attractor of a BN is a set of states satisfying that any state in this set can be reached from any other state in this set and no state in this set can reach any other state that is not in this set.

[Attractor system] An attractor together with its state transition relations is referred to as an attractor system.

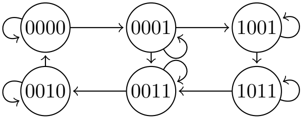
Three types of attractor systems for asynchronous BNs (BSCCs):



(a) A selfloop



(b) A simple loop



(c) A complex loop

BDD-based attractor detection for asynchronous BNs

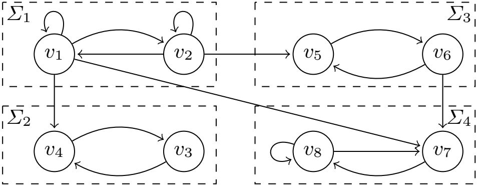
[Block] Given a BN $G(V, \boldsymbol{f})$ with $V = \{v_1, v_2, \ldots, v_n\}$ and $\boldsymbol{f} = \{f_1, f_2, \ldots, f_n\}$, a block $B(V^B, \boldsymbol{f^B})$ is a subset of the network, where $V^B \subseteq V$. For any node $v_i \in V^B$, if B contains all the parent nodes of v_i, its Boolean function in B remains the same as in G, i.e., f_i; otherwise, the Boolean function is undetermined, meaning that additional information is required to determine the value of v_i in B.

We call the nodes with undetermined Boolean functions as undetermined nodes.

We refer to a block as an elementary block if it contains no undetermined nodes.

BDD-based attractor detection for asynchronous BNs

Our decomposition method:



- An elementary block contains no undetermined nodes.
- Given a BN G, let B be an elementary block in G. B preserves the attractors of G.

BDD-based attractor detection for asynchronous BNs

[Projection map, Compressed state, Mirror states] For a BN G and its block B, where the set of nodes in B is $V^B = \{v_1, v_2, \ldots, v_m\}$ and the set of nodes in G is $V = \{v_1, v_2, \ldots, v_m, v_{m+1}, \ldots, v_n\}$, the projection map $\pi_B : X \to X^B$ is given by $\boldsymbol{x} = (x_1, x_2, \ldots, x_m, x_{m+1}, \ldots, x_n) \mapsto \pi_B(\boldsymbol{x}) = (x_1, x_2, \ldots, x_m)$.

For any set of states $S \subseteq X$, we define $\pi_B(S) = \{\pi_B(\boldsymbol{x}) : \boldsymbol{x} \in S\}$. The projected state $\pi_B(\boldsymbol{x})$ is called a compressed state of $\boldsymbol{x}$. For any state $\boldsymbol{x}^B \in X^B$, we define its set of mirror states in G as $\mathcal{M}_G(\boldsymbol{x}^B) = \{\boldsymbol{x} \mid \pi_B(\boldsymbol{x}) = \boldsymbol{x}^B\}$. For any set of states $S^B \subseteq X^B$, its set of mirror states is $\mathcal{M}_G(S^B) = \{\boldsymbol{x} \mid \pi_B(\boldsymbol{x}) \in S^B\}$.

BDD-based attractor detection for asynchronous BNs

[Preservation of attractors] Given a BN G and an elementary block B in G, let $\mathcal{A} = \{A_1, A_2, \ldots, A_m\}$ be the set of attractors of G and $\mathcal{A}^B = \{A_1^B, A_2^B, \ldots, A_{m'}^B\}$ be the set of attractors of B. We say that B preserves the attractors of G if for any $k \in [1, m]$, there is an attractor $A_{k'}^B \in \mathcal{A}^B$ such that $\pi_B(A_k) \subseteq A_{k'}^B$.

BDD-based attractor detection for asynchronous BNs

[Preservation of attractors] Given a BN G and an elementary block B in G, let $\mathcal{A} = \{A_1, A_2, \ldots, A_m\}$ be the set of attractors of G and $\mathcal{A}^B = \{A_1^B, A_2^B, \ldots, A_{m'}^B\}$ be the set of attractors of B. We say that B preserves the attractors of G if for any $k \in [1, m]$, there is an attractor $A_{k'}^B \in \mathcal{A}^B$ such that $\pi_B(A_k) \subseteq A_{k'}^B$.

Lemma

Given a BN G and an elementary block B in G, let Φ be the set of attractor states of G and Φ^B be the set of attractor states of B. If B preserves the attractors of G, then $\Phi \subseteq \mathcal{M}_G(\Phi^B)$.

Theorem

Given a BN G, let B be an elementary block in G. B preserves the attractors of G.

BDD-based attractor detection for asynchronous BNs

[Crossability, Cross operations]

- B_i – a non-elementary block,
  $V^{B_i} = \{v_{p_1}, v_{p_2}, \ldots, v_{p_s}, v_{q_1}, v_{q_2}, \ldots, v_{q_t}\}$
- B_j – B_i's parent block,
  $V^{B_j} = \{v_{q_1}, v_{q_2}, \ldots, v_{q_t}, v_{r_1}, v_{r_2}, \ldots, v_{r_u}\}$
- $\boldsymbol{x}^{B_i} = (x_1, x_2, \ldots, x_s, y^i_1, y^i_2, \ldots, y^i_t)$ a state of B_i
- $\boldsymbol{x}^{B_j} = (y^j_1, y^j_2, \ldots, y^j_t, z_1, z_2, \ldots, z_u)$ a state of B_j
- Crossable: $\boldsymbol{x}^{B_i} \ \mathcal{C} \ \boldsymbol{x}^{B_j}$, if the values of their common nodes are the same, i.e., $y^i_k = y^j_k$ for all $k \in [1, t]$.
- The cross operation:
  $\Pi(\boldsymbol{x}^{B_i}, \boldsymbol{x}^{B_j}) = (x_1, x_2, \ldots, x_s, y^i_1, y^i_2, \ldots, y^i_t, z_1, z_2, \ldots, z_u)$

BDD-based attractor detection for asynchronous BNs

[Crossability, Cross operations]
We say a set of states $S^{B_i} \subseteq X^{B_i}$ and a set of states $S^{B_j} \subseteq X^{B_j}$ are crossable, denoted as $S^{B_i} \mathcal{C} S^{B_j}$, if at least one of the sets is empty or the following two conditions hold: 1) for any state $\boldsymbol{x}^{B_i} \in S^{B_i}$, there always exists a state $\boldsymbol{x}^{B_j} \in S^{B_j}$ such that $\boldsymbol{x}^{B_i}$ and $\boldsymbol{x}^{B_j}$ are crossable; 2) vice versa.

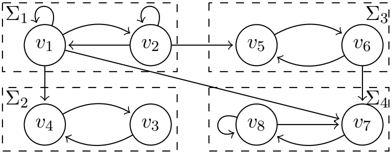
$\Pi(S^{B_i}, S^{B_j}) = \{\Pi(\boldsymbol{x}^{B_i}, \boldsymbol{x}^{B_j}) \mid \boldsymbol{x}^{B_i} \in S^{B_i}, \boldsymbol{x}^{B_j} \in S^{B_j}$ and $\boldsymbol{x}^{B_i} \mathcal{C} \boldsymbol{x}^{B_j}\}$.

Let $\mathcal{S}^{B_i} = \{S^{B_i} \mid S^{B_i} \subseteq X^{B_i}\}$ be a family of states sets in B_i and $\mathcal{S}^{B_j} = \{S^{B_j} \mid S^{B_j} \subseteq X^{B_j}\}$ be a family of states sets in B_j. We say $\mathcal{S}^{B_i}$ and $\mathcal{S}^{B_j}$ are crossable, denoted as $\mathcal{S}^{B_i} \mathcal{C} \mathcal{S}^{B_j}$ if for any states set $S^{B_i} \in \mathcal{S}^{B_i}$, there always exists a states set $S^{B_j} \in \mathcal{S}^{B_j}$ such that S^{B_i} and S^{B_j} are crossable; 2) vice versa.

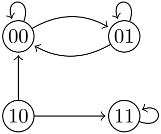
$\Pi(\mathcal{S}^{B_i}, \mathcal{S}^{B_j}) = \{\Pi(S_i, S_j) \mid S_i \in \mathcal{S}^{B_i}, S_j \in \mathcal{S}^{B_j}$ and $S_i \mathcal{C} S_j\}$.

BDD-based attractor detection for asynchronous BNs

[Realisation of a block]



(a) SCC decomposition of a BN.



(b) Transition graph of B_1.

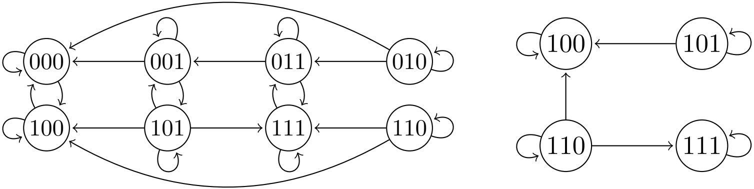


Figure: Transition graphs of two realisations of B_3.

BDD-based attractor detection for asynchronous BNs

Main theorem

[Crossability of attractors] Let B_i be a single and elementary parent block of a non-elementary block B_j in a BN G. Let A^{B_i} be an attractor of B_i and let A^{B_j} be an attractor in the realisation of B_j with respect to A^{B_i}. Then $A^{B_i} \ \mathcal{C} \ A^{B_j}$.

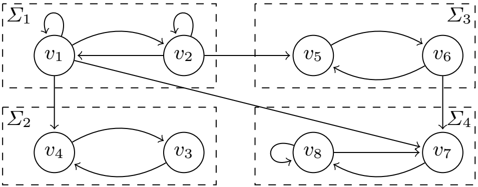
[Attractor recovery] Given a BN G with B_i and B_j being its two blocks, let $\mathcal{A}^{B_i}$ and $\mathcal{A}^{B_j}$ be the set of attractors for B_i and B_j, respectively.
Let $B_{i,j}$ be the block got by merging the nodes in B_i and B_j. If B_i and B_j are both elementary blocks or B_i is an elementary and single parent block of B_j, then $\mathcal{A}^{B_i} \ \mathcal{C} \ \mathcal{A}^{B_j}$ and $\Pi(\mathcal{A}^{B_i}, \mathcal{A}^{B_j})$ is the set of attractors of $B_{i,j}$.

BDD-based attractor detection for asynchronous BNs

Corollary

Given a BN G *with* B_i*,* B_j*, and* B_k *being its three blocks, let* $\mathcal{A}^{B_i}$*,* $\mathcal{A}^{B_j}$*, and* $\mathcal{A}^{B_k}$ *be the sets of attractors for blocks* B_i*,* B_j*, and* B_k*, respectively. If the three blocks are all elementary blocks or* B_i *is an elementary block and it is the only parent block of* B_j *and* B_k*, it holds that* $\Pi(\Pi(\mathcal{A}^{B_i}, \mathcal{A}^{B_j}), \mathcal{A}^{B_k}) = \Pi(\Pi(\mathcal{A}^{B_i}, \mathcal{A}^{B_k}), \mathcal{A}^{B_j})$*.*

BDD-based attractor detection for asynchronous BNs



- Compute the attractors of the elementary block B_1.
- For B_2, form realisations of B_2 with the attractors of B_1, then compute attractor of each of the realisations.
- Similarly, compute the attractors for B_3.
- B_4 has two parent blocks: merge B_1 and B_3 as its new parent block, and compute its attractors.
- Similarly, compute the attractors for B_4.
- Recover the attractors of the BN by cross operations.

BDD-based attractor detection for asynchronous BNs

Evaluation: MAPK network (53 nodes) & apoptosis (97 nodes)

Networks	# attractors	Time(s)		Speedup	Networks	# attractors	Time(s)		Speedup
		Alg. 1	Alg. 2				Alg. 1	Alg. 2	
MAPK_r3	20	6.070	2.614	2.32	apoptosis	1024	1633.970	103.856	15.73
MAPK_r4	24	11.674	1.949	5.99	apoptosis*	2048	8564.680	218.230	39.25

BDD-based attractor detection for asynchronous BNs

MAPK network

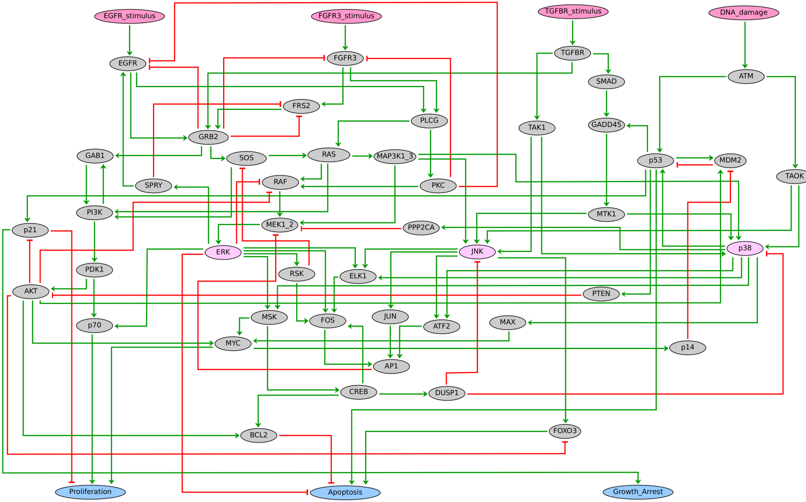
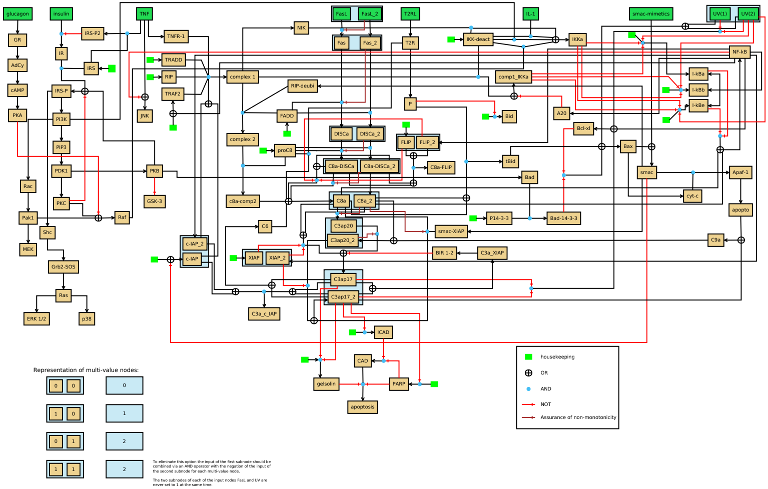


Image: L. Grieco et al. *PLOS Computational Biology*, 9(10):e1003286, 2013.

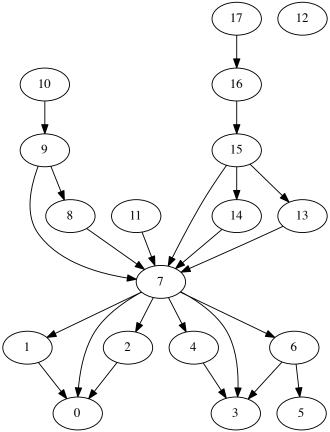
BDD-based attractor detection for asynchronous BNs

Apoptosis network



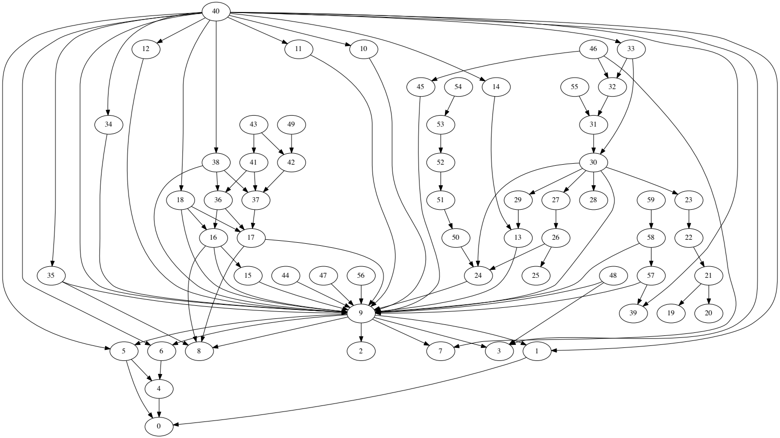
BDD-based attractor detection for asynchronous BNs

MAPK network SCC decomposition



BDD-based attractor detection for asynchronous BNs

Apoptosis network SCC decomposition



Software tool: ASSA-PBN

ASSA-PBN

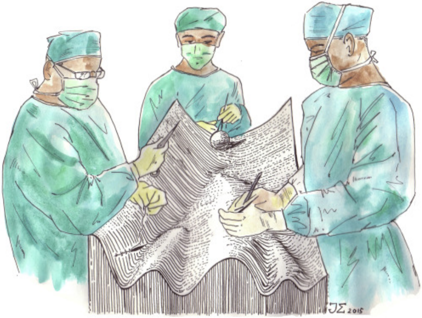
Approximate **S**tead-**S**tate **A**nalyser-PBN

a software tool for modelling, simulation and analysis of probabilistic Boolean networks

Freely available at

`http://satoss.uni.lu/software/ASSA-PBN/`

Future perspectives



Scalable control of large biological networks!

- Network controllability (e.g., minimal interventions driving the system from a certain attractor to a specific target attractor)
- Two running projects: SEC-PBN and AlgoReCell

Image: S. J. Häfner and A. H. Lund. *Biomedical Journal*, 39(3):166–176, 2016.

Acknowledgements

Jun Pang

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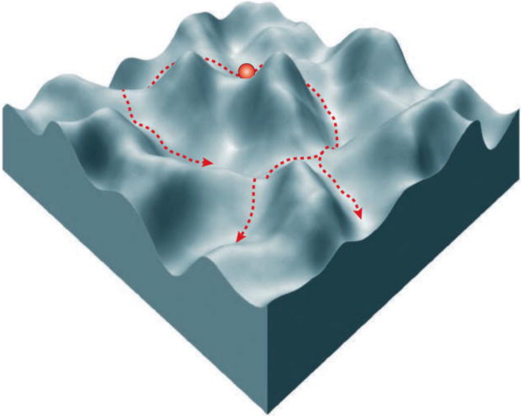

Thank you for your attention!